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REPORT ON CHROMOSOME 6

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The fact that chromosome 6 is singled out for a report on its own shows that this is an area of increasing activity and interest, stimulated by the assignment of the HLA region to chromosome 6. This assignment is now fully confirmed by direct detection of HLA segregation in man-mouse somatic cell hybrids[13,24]. Following the recent 6th International Histocompatibility Testing Workshop in Aarhus[12], the nomenclature of the HLA region has been somewhat revised to take account of the increasing number of loci being assigned to the region, as indicated in Table 1.

An overall summary of the mapping data on chromosome 6, including HLA fine structure, is given in Figure 1. The main advances since the 2nd Human Gene Mapping Conference are:

(1) The assignment of GLO to this linkage group [11,17,27]. Combined lod scores for GLO-HLA are given in Table II. Somatic cell data[2] show only two exceptions (one clearly due to chromosome breakage) to GLO and chromosome 6 segregation in 15 independent man-mouse hybrids and no consistent segregation with any other chromosome.

(2) The detection of linkage between PGM-3 and the centromere using ovarian teratomas[22]. This provides the first clue to the possible orientation of the HLA region in relation to the centromere.

(3) A great increase in knowledge concerning the fine structure mapping of the HLA region, including especially the assignment to it of genes controlling the second[7], fourth [12] and eighth[19] complement components and the Rodgers blood group[8]. The 6th Histocompatibility Testing Workshop[12], in addition gave rise to a much better definition of the MLC determinants controlled by the HLA-D locus. So far it is only C2, C4 and C8 levels that are controlled by genes in the HLA region, which leaves open the question as to whether any of the relevant structural genes are in the region. Only for C2 is the data good enough to indicate a location for the relevant gene[7]. (see Figure 1). Bf, Ch and Rg map near the HLA-B and C loci, with some question as to how far to the left of B is the Bf locus. Data on recombination between these three markers and HLA-A or B are given in Table V. The Rg- allele is in strong linkage disequilibrium with

B8 and in significant linkage disequilibrium with BW40 (formerly W10) and Bf^{S} [8]. The Ch- allele is in significant linkage disequilibrium with B12 and BW35 (formerly W5) [9,18].

Further data have added to the lod scores between PGM-3 and HLA, as indicated in Table III. A summary of some negative lod scores for exclusion of linkage with HLA is given in Table IV. So far there are only very limited data on regional assignment of the markers within chromosome 6, a deficiency which will surely soon be remedied by the use of chromosome variants in hybrids.

TABLE I

The HLA region : New and old nomenclature

	New	Old
Region name	HLA	HL-A
Loci	HLA-A	LA or 1
	HLA-B	FOUR or 2
	HLA-C	AJ or 3
	HLA-D	MLC-1, etc.

Other products or functions:

Chido (Ch) and Rodgers (Rg) blood groups.

Bf, C2, C4, C8 - Complement functions.

Immune response, Disease susceptibility,

'Ia' antigens.

TABLE II

Lod Scores for HLA-GLO

Source	θ =	0.05	0.10	0.20	0.30	0.40
Rochester	Paternal	1.98	2.91	2.86	1.92	0.75
Rochester	Maternal	3.31	3.08	2.30	1.38	0.50
Seattle-Wpg	Paternal	0.63	0.75	0.66	0.42	0.15
Seattle-Wpg	Maternal	~~0.81~~ 1.73	~~0.72~~ 1.84	~~0.52~~ 1.43	~~0.30~~ 0.81	~~0.09~~ 0.24
Seattle-Wpg	Intercross	0.58	0.70	0.46	0.18	0.04
	Total	~~6.48~~ 8.23	~~7.41~~ 9.28	~~6.14~~ 7.71	~~3.78~~ 4.71	~~1.38~~ 1.68

= 5.68

Sources: This meeting, refs. 27,17,11.

TABLE III

Lodscores for HLA - PGM-3

	R	NR	θ=0.05	0.10	0.20	0.30	0.40	$\hat{\theta}$	Reference
Male	-	-	6.03	7.29	6.38	4.02	1.46	0.11	16
	7	34	1.37	5.10	6.59	5.35	2.83	0.11	10
	-	-		1.94	1.44	0.88	0.30		3
Sum				14.33	14.41	10.25	4.59	~0.15	
Female	-	-	-9.73	-5.07	-1.39	-0.20	0.03	0.4	16
	7	11	-12.39	-6.74	-2.14	-0.42	-0.11	0.43	10
	-	-		-1.31	-0.46	-0.14	-0.22		3
Sum				-13.09	-3.99	-0.76	-0.10		

Σ = -13.12

-.30

TABLE IV

Paternal Lods for HLA < - 2

At 0

0.05	:	Co
0.10	:	ADA, AK-1, AMY, E1, Gm, Hbβ, Inv, PGD, Pi, Pr
0.20	:	AcP-1, C3, ESD, Fy, Gc, GPT, GT, Hp, Jk, Kell, Le, Lu, P
0.30	:	ABO, MNSs, PGM-1, Rh, Se.

Sources : References 16, 17, 26 (This list is not exhaustive)

TABLE V

Recombination between Chido (Ch), Rodgers (Rg) or Bf and HLA-A or B

	Recombinants	Non-recombinants	References
Ch : HLA-B	0	139	9, 18, 17
Rg : HLA-A, B or Bf	0	105	8
Bf : HLA-B	0	219	20 Lamm, L (in press)
Bf : HLA-A, B or C	3	120	23
	0	44	1

FIG. 1

Chromosome 6 Mapping

Pairwise Linkages

(centromere) O	17 [a]	PGM-3	95% limits: 7-34	P [b] (22)
GLO	10	HLA	lod = 7.4	F,S : C (11,17,27)
HLA	20	Pg-5	lod = 3.5	F : P (25,27)
PGM-3	15 (male)	HLA	lod = 14.4	F, S : C (3,10,16)

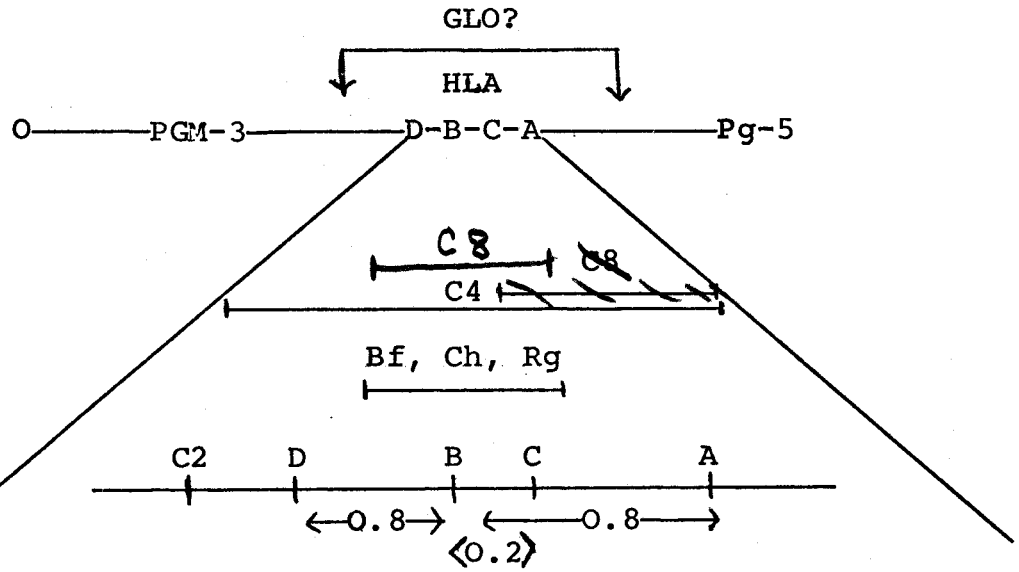
Also on 6 : ME-1, SOD-1 S : C

Regional Localization

Exclusions (Deletion or translocation) 6pter ■ 6p22 —O— 6q27 ■ 6qter (4,5,6)

Inclusion (Inversion) 6p22 ▭O▭ 6q23 (15)

Tentative Map [c]



HLA region Map [d]

(There are two C8 - HLA - A recombinants and no C8 - HLA - B recombinants DM Bodmer)

Footnotes to Fig. 1

(a) Map distances are given in cM.

(b) P = Provisional, C = Confirmed, F = Family, S = Somatic Cells.

(c) The arm of this linkage group cannot yet be determined. The orientations of PGM-3, HLA, Pg-5 and the centromere are based on the relative map distances, which are still clearly subject to a substantial margin of error. Direct mapping of HLA to the centromere using ovarian teratomas should readily establish whether the given order is correct. The orientation of the HLA region with respect to PGM-3 is based on the data of Lamm et al[14a]. The uncertainty for GLO arises from a conflict between the data of Kompf et al[14], which shows substantial negative lods with PGM-3 and that of Weitkamp et al (this conference)[27], which suggests, from HLA recombinants, that GLO is on the B side of HLA.

(d) This HLA region map is a summary assessment from a number of sources including especially, for Bf, Ch, Rg and C8 papers in this volume[8, 9, 19, 20], for A, B, C, D and C4 papers in Histocompatibility Testing 1975[12], and for C2, Fu et al[7]. No attempt has been made to include incompletely defined markers such as those for disease association and immune response, 'Ia' like antigens or the proposed second 'weak' MLC locus.

Numbers in parentheses refer to relevant references in this volume and elsewhere, as listed at the end of this report.

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